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THE REDUPLICATION HYPOTHESIS AS APPLIED TO DROSOPHILA

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A NUMBER of papers developing the reduplication hypothesis of linkage have recently appeared in the *Journal of Genetics*. They are based almost entirely on the experiments of Gregory ('11) on *Primula* and of Punnett ('13) on the sweet pea. The data are not entirely satisfactory because of the relatively small number of genes involved, and because in most cases the gametic ratios can be only approximately determined. This is due to the fact that most of the data concern F_2 counts, from which gametic ratios can not be calculated directly. In Gregory's best case a much more satisfactory method was followed—the heterozygous plants were tested, not by mating to others of their kind, but by crossing with plants recessive with respect to all the genes involved, which gives the gametic ratio directly. In this case, however, we have only a relatively small series of data involving as many as three pairs of linked genes. It is obvious that from such data no adequate test of the reduplication hypothesis can be made.

The phenomena of linkage have been very extensively studied, by Morgan and others, in the fly *Drosophila*. In this animal there are many genes belonging to the same linkage groups, and these have been studied on a large scale. In the case of the sex-linked group there is never any difficulty in calculating the gametic ratio from F_2 results, since the F_2 males from any cross always give it directly. I have recently published a paper (Sturtevant, '14) giving a complete summary of the published results obtained from studies of the linkage of these genes. In that paper I have adopted the chromosome explanation of linkage proposed by Morgan ('11). Here I shall use the same data for a test of the reduplication theory. It may be of value to contrast the two views by making a rigorous application of them to the same facts. Since the data concerning the sex-linked group of genes in *Drosophila* form the simplest and most extensive series now available, I shall deal more especially with them. The reader is referred to my other paper for the detailed data, for references to original sources, and for a full treatment of the chromosome hypothesis as applied to these and other data.

It may be well to give first a brief catalogue of the sex-linked genes discussed in this paper. The nomenclature is that suggested by Morgan ('13). This may be confusing to those accustomed to the "presence and absence" system, but this should not be a serious objection here, since a clear conception of the somatic appearance of the animals discussed is not essential for our present purpose. The relations would be as clear if hieroglyphics were used for symbols.

Y is the gene which differentiates the wild "gray" bodied fly from the yellow mutant, *y*.

V differentiates the wild red-eyed fly from the vermilion-eyed mutant, *v*.

M differentiates the "long" wing of the wild fly from that of the miniature-winged mutant, *m*.

R is another gene affecting the wings. The wild fly has *R*, the rudimentary-winged mutant has *r*.

Br′ occurs in a dominant mutant form having a narrow eye known as barred. The allelomorph present in the wild fly is designated *br′*.

The other characters concerned bear such a relation to one another that the genes involved are considered as forming a system of quadruple allelomorphs. The alternative to this view is the assumption of complete linkage, but I have given elsewhere (Sturtevant, '13) my reasons for preferring the multiple allelomorph interpretation. The eye of the wild *Drosophila* is red in color. A single mutant obtained from it had white eyes (Morgan, '10), and this character proved to be a simple sex-linked recessive. From the white-eyed form arose a fly with eosin eyes (Morgan, '12). This new character was found to be a sex-linked dominant to white, and a sex-linked recessive to red. Finally, there arose a form with cherry eye color (Safir, '13). This has the same relation to red and to white as has eosin. Mated to eosin it gives an intermediate color, which splits up into cherry, intermediate, and eosin in F_2. The nomenclature adopted in this case is as follows:

Allelomorph present in the red-eyed fly, W.
Allelomorph present in the white-eyed fly, w.
Allelomorph present in the eosin-eyed fly, w^e.
Allelomorph present in the cherry-eyed fly, w^c.

Trow ('13) has suggested the possibility of an asymmetrical reduplication series, giving a gametic series of $wAB:xAb:yaB:zab$, where w need not equal z, nor x equal y. It should be noted that an actual demonstration of such a ratio, or of its non-existence, is almost excluded for the reason that it would be practically impossible to be sure one was not dealing with a case involving differential viability. However, perhaps the most striking general fact brought out by the study of linkage is that each pair of linked genes (allelomorphs), considered separately, follows a perfectly regular Mendelian course. I think we are, therefore, justified in assuming that the number of gametes bearing A is always equal to the number bearing a, and similarly for B and b. Then, in Trow's asymmetrical series,

$$w+x=y+z,$$
$$w+y=x+z.$$

Hence,

$$w=z \quad \text{and} \quad x=y.$$

In all that follows I shall assume that the reduplication series are always symmetrical. On this assumption it becomes unnecessary to consider the two halves of the series separately, and I shall therefore use only two terms in speaking of gametic ratios. By adding together the two halves of the series larger numbers are obtained, so that chance deviations are relatively smaller. Differential viability is also partially overcome in this way. Of course on the reduplication theory both terms of the gametic ratio must be integers, since they represent numbers of cells, but nevertheless it has seemed to me more convenient for purposes of calculation to express them always in the form $n:1$. Thus a gametic ration of $3:2$ may be written $1.5:1$.

It was suggested by Bateson and Punnett ('11) that the intensity of coupling and of repulsion between the same two pairs of genes may be identical. That this is substantially the case has been shown again and again in *Drosophila,* and has become a truism among those working on that form. Before presenting data on this point I wish to bring up another matter on which the same data have a bearing. Punnett ('13) has said, "But where three [pairs of] factors are concerned . . . the value of the primary reduplications is evidently altered, and there would seem to be some process whereby these reduplications react on one another." Bailey ('14) has suggested that the nature of this interaction may be such as to cause the two primary series to be of equal intensity. It may be categorically stated that *there is no interaction effect in Drosophila.* The best data for a test of the relative intensity of coupling and repulsion, and of "fundamental," "primary" and "secondary" reduplication series, involving the same allelomorphic groups, is that furnished by the relations of the various forms of W (W, w, w^e, w^c) to the M pair of allelomorphs (M and m). Table I is a summary of the data on this case. In computing the fundamental series I have used only the data from such of my own experiments as involve only two pairs of genes, since that from other sources is for the most part made up of primary series in which the other primary series involved is masked.

TABLE I

FUNDAMENTAL SERIES

Nature of Cross	Actual Numbers	Gametic Ratios
$WM \times wm$	777: 470	1.6 +: 1
$Wm \times wM$	93: 221	1: 2.4 —
$WM \times w^em$	634: 348	1.8 +: 1
$Wm \times w^eM$	46: 110	1: 2.4 —
$Wm \times w^cM$	461: 855	1: 1.9 —
$w^eM \times wm$	4,171: 1,858	2.2 +: 1
$w^em \times wM$	891: 1,898	1: 2.1 +
$w^cM \times wm$	75: 47	1.6: 1

PRIMARY SERIES

Nature of Cross	Actual Numbers	Gametic Ratio	Other Primary Series Involved
$WM \times w^em$	178: 85	2.1 —: 1	*MBr′*
$w^em \times wM$	69: 122	1: 1.8 —	*MBr′*
$WM \times wm$	5,838: 2,911	2.0 +: 1	*YW*
$Wm \times wM$	1,111: 2,493	1: 2.2 +	*YW*
$WM \times wm$	2,261: 1,011	2.2 +: 1	*MR*

	Secondary Series		Primary Series
$WM \times w^em$	719: 407	1.8 —: 1	*WV, VM*
$Wm \times w^eM$	227: 509	1: 2.2 —	WV, VM

It will be noted that in all these cases the gametic ratio approximates 2:1, or 1:2, according to the nature of the cross. There are only four cases showing a noticeable deviation from this value, and of these two involve only small counts. The most serious is the first. In this case there is a deviation of 54.3 from the 2:1 ratio, and the standard error is $16.7[\sqrt{1/3 \times 2/3 \times (777 + 470)} = \pm 16.7-]$. Since the deviation is slightly over three times the standard error, it is perhaps significant, especially since there is at least one other rather large deviation (the second ratio in Table I). For our present purpose, however, it is probably not significant, since similar deviations occur in different experiments of exactly the same type. I have recorded elsewhere (Sturtevant, '14) the results of a number of tests of individual females heterozygous for these two allelomorphic groups. Taking only those cultures which produced 100 or more flies, we find the following results:

Seven females of the constitution $w^e m w M$ gave gametic ratios ranging from 1.5:1 to 2.7:1, with the modal class at about 2.0:1.

Seventeen females $w^e M w m$ gave ratios ranging from 1.5:1 to 3.4:1, with a single individual at 4.2:1. The modal class was at about 2.2:1.

It seems highly probable that all these deviations from a 2:1 ratio, not due to insufficient numbers, may be satisfactorily explained on the basis of differential viability, which is known to occur here (for a discussion of the vagaries of differential viability see Bridges and Sturtevant, '14). I do not wish to be understood as arguing that the gametic ratio for any two pairs of genes is absolutely constant, but only that it is in most cases uninfluenced by the way in which the genes are combined and by heterozygosis for other genes. That it may sometimes show marked differences is now well established. I have myself studied two cases of this sort, and I have good evidence (not yet published in detail) that there are definite genes which cause great differences in the gametic ratios for whole linkage groups. In one case this gene itself shows linkage to those in the group it affects. But even here the intensity of coupling and of repulsion is affected alike, and it makes no difference how few or how many genes a fly is heterozygous for; the linkage is strong or weak according to the form of the linkage-affecting gene which the fly happens to carry. In each of these cases I have been able to obtain about the same extreme values both for coupling and for repulsion.

In what follows I shall assume that the intensity of the reduplication series is not affected by the way in which the genes are introduced, nor by the number of linked genes involved in the cross. The obvious corollary of this is that reduplication occurs even in homozygous individuals, and that the nature of the series of divisions is in general independent of the constitution of the individual. This conclusion is directly opposed to the point of view expressed more especially by Punnett, in the passage quoted above and elsewhere. If reduplication occurs at all it is the same in the wild fly as in the most complex linkage experiment we have yet carried out.

If it is assumed that the intensity of coupling and repulsion is identical, it becomes unnecessary to consider them separately. I shall therefore lump together all the data involving the same groups of allelomorphs, regardless of how they were put into the cross. When three pairs of genes are involved there are eight possible combinations of them in F_2, but only four if we add together the two halves of the reduplication diagram. There are the two original combinations, which I shall designate *ABC*. Then there are three combinations derived from each of these by a shifting of one gene, which I shall designate *ABc*, *AbC* and *aBC*, the small letters referring to those pairs which have been shifted. Thus, to take an imaginary case, if we cross *LMn* by *lmN*, the gametes produced by the F_1 individuals will be classified as follows:

ABC	*ABc*	*AbC*	*aBC*
LMn	*LMN*	*Lmn*	*lMn*
lmN	*lmn*	*lMN*	*LmN*

In the following tables I shall reduce all data to this form. In each case the genes will be arranged so that *AB* and *BC* will be the primary reduplication series.[1]

Table II contains such a summary of all the crosses involving three pairs of sex-linked genes. Table III shows the gametic ratios derived from these data, and also the values for the secondary series calculated on the basis of Trow's "special" hypothesis. For the sake of brevity only one term is used: a gametic ratio of 3:1 is written 3; a ratio of 3:2 becomes 1.5, etc. With the simplifications introduced here Trow's formula becomes

$$AC = \frac{(AB \times BC) + 1}{AB + BC}.$$

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[1] As was pointed out by Punnett ('13), in a system of three reduplication series the one with the lowest intensity is to be regarded as the secondary series.

TABLE II

Allelomorphic Groups	*ABC*	*ABc*	*AbC*	*aBC*
YWM	8,212	4,013	9	119
YWR	278	160	0	1
YVM	1,082	58	22	665
YVR	315	138	55	196
YVBr′	93	34	10	54
WVM	194	11	1	102
WMR	1,726	535	139	872
WMBr′	220	73	25	129

TABLE III

Experiment	Gametic ratios			
	Observed			Calculated
	AB	*BC*	*AC*	*AC*
YWM	95.5	2.1	2.0 −	2.0 +
YWR	438.0	1.74	1.72	1.74
YVM	1.7	22.0	1.5	1.6
YVR	1.8	2.6	1.1	1.3
YVBr′	2.0	3.4	1.3	1.4
WVM	2.0	24.7	1.7	1.9
WMR	2.2	3.9	1.3	1.6
WMBr′	1.9	3.6	1.2	1.4

It will be seen that in every case the calculated value for the secondary reduplication is higher than the observed value. The same relation comes out in two experiments which I have done involving genes of another group in *Drosophila* (see Table VIII, Sturtevant, '14). Punnett's case is so involved that calculations accurate enough for our present purpose can not be made. In Gregory's experiment one of the genes (M) could not be followed in all the plants because masked by another gene. We are not given the data for S and G in those plants in which M was classified separately from those in which it was not. The data are therefore not available for exact calculations, since the numbers are too small to overcome chance deviations. The data for my own two experiments appear in Table IV.

The same relation comes out more strikingly in another way. If we let m equal the intensity of the AB series and n that of the BC series, then on Trow's special hypothesis the four kinds of gametes should occur in the following proportions:

$$\begin{aligned} ABC &- mn \\ ABc &- m \\ aBC &- n \\ AbC &- 1 \end{aligned}$$

TABLE IV

Experiment	Observed			Calculated
	AB	BC	AC	AC
BVgCv................	3.4	11.6	2.4	2.7
BCvSp................	2.5	2.1	1.0	1.4

That is, $1/(m+1)$ of the gametes should have A and B interchanged. Of these, $1/(n+1)$ should have B and C also interchanged. If N represents the total number of gametes, then the size of the AbC class should be represented by the expression

$$AbC = \frac{N}{(m+1)(n+1)}.$$

Table V shows the relation between the size of this class as observed and as thus calculated, in the ten experiments.

TABLE V

Allelomorphic Groups	ABC Observed	ABC Calculated
YWM	9	42
YWR	0	0
YVM	22	30
YVR	55	69
YVBr′	10	15
WVM	1	4
WMR	139	208
WMBr′	25	34
BVgCv	2	7
BCvSp	12	20

Thus it appears that in all ten experiments Trow's formula gives values for the AC series and for the AbC

term which are too large. Moreover, this feature appears in a more complex cross which I have carried out, involving four pairs of linked genes (*YWVM*), and in each separate part of all these experiments, regardless of how the crosses were made. It may, then, be taken as a constant relation. It can only mean that there is some relation between *A* and *C* besides that resulting from secondary reduplication. In other words, to use Bailey's terms, Trow's "special" hypothesis is not valid.

Let us then examine what Bailey calls Trow's "general" hypothesis. Suppose the primary series to be of the following values:

$$\begin{aligned} AB &= l:1, \\ BC &= m:1, \\ AC &= n:1. \end{aligned}$$

Trow's general formula for calculating what should be the observed value of the *AC* series is

$$AC = \frac{lmn + n}{l + m}.$$

The special formula is derived from this by assuming $n = 1$, when the formula becomes

$$AC = \frac{lm + 1}{l + m}.$$

Since this always gives a value which is too large, it follows that n is always less than one. This means that the *AC* primary series is reversed—that the combinations present in the parents tend to be reproduced in fewer numbers than the new combinations. I have worked this out for the case of *BCvSp* (see Table IV), and find the primary series there to be 0.6 : 1, though the observed series is 1.0. The "fundamental" *AC* series has been obtained for most of the cases in Table III, and has always been found to be of the usual form (*i. e.*, $n:1$, where $n > 1$). (See Table I, Sturtevant, '14.) In fact, as stated above, the fundamental series always approximates the secondary (observed) series.

There are two hypotheses as to the mechanics of reduplication series where more than two pairs of genes are involved. The first was suggested by Bateson and Punnett ('11), and consists in the assumption that when three pairs are involved eight cells are formed by three successive divisions, each of which segregates one pair of genes. The eight cells then represent the eight possible kinds of gametes, and are supposed to reduplicate independently until the proper proportions are reached. Bailey supposes that if it be shown that two primary series do not interact on each other this scheme will be more likely to be correct than will Trow's, which I shall discuss next. It seems to me, however, that this hypothesis begs the question. It is derived entirely by working backwards from the observed results; it affords no basis for predictions; and it does not offer a simple mechanical explanation of any of the observed results. For pragmatic reasons I believe we should adopt it only as a last resort.

Trow supposes that two cell divisions occur, segregating two pairs of genes. The four resulting cells then go through with their reduplication, which is a primary one. When this is finished there occur divisions which segregate the other pair, and the other primary reduplication is carried out. On Trow's general hypothesis, which I have tried to show is the only one which can hold, it is supposed that the second series of reduplications is affected by both of the first two pairs of genes. *C* is reduplicating more if with *B* than if with *b*, less if with *A* than if with *a*. This scheme of Trow's has one great advantage in that it accounts for the fact that the class which I have called *AbC* is always the smallest one. Reference to Trow's calculations will show that this relation should always occur, and Table II shows that it does occur. On the octant scheme there is no explanation of this relation—we simply have to assume that it does occur somehow.

It will be noted that several of the gametic ratios involved here closely approach 2:1. *YV, YM, WV* and *WM* are the most conspicuous examples. It may seem that such a simple ratio is due to a very simple reduplication series, but I do not think such an assumption can be successfully maintained. The tables given above show that *YM* and *WM* have approximately this same value when they appear as secondary series, and the data for the combination *YWVM* show the same thing for *YV* (see Sturtevant, '14).

If, as I have maintained above, the same series of reduplications must occur in all flies, whether we can follow it or not, then it follows that in these three cases the 2:1 ratio is never due to a simple series, but always to a long and complicated one, since in all three one of the primary series is of high intensity.

It was pointed out by Trow that the intensities of the reduplication series afford a method of calculating the number of cell divisions necessary to complete the series. If we assume that approximately the same series is occurring both in homozygous and in heterozygous flies, we have the following series in *Drosophila* as a basis for such calculations.

Sex-linked Group

YW = 90.1
WV = 2.1
VM = 31.8
MR = 5.0
RBr = 21.7

Second Group

BVg = 3.6
VgCv = 10.4
CvSp = 2.8
SpBa = 10 +

Third Group

PEb = 100 ±

All of these series must be considered as either primary or secondary and therefore involving primaries of higher intensity. In fact there is unpublished evidence that many of them can not be simple primaries. A number of series of very high intensity are known, and will appear in future publications. Therefore all the calculations that follow give results which are far too small.

According to Trow, the minimal number of successive cell divisions required to complete the series is given by the expression $mnp \cdots$ where m, n, p, etc., are the larger terms of the primary series involved. In the present case the value of that expression is something over 76,000,000,000. However, Trow's formula seems to be wrong. If a be the number of cell divisions required to produce m cells, then $2^a = m$. If this expression gives a value of a which is not an integer, then the next higher whole number is to be taken. In the case of the first series two divisions are necessary to segregate the genes, and in the following series one is required. The number of successive cell divisions required then is $(a+1) + (b+1) + (c+1) + \cdots + 1$, where b, c, etc., bear the same relation to n, p, etc., that a does to m. In the case of *Drosophila* the value of this expression is 56. As pointed out, however, this value is certainly far too small.

The total number of cells required is given by the expression $2mnp \cdots + 2np \cdots + 2mn \cdots + 2mp \cdots + 2m \cdots + 2n \cdots + 2p \cdots + \cdots + 2mnp + 2mn + 2mp + 2np + \cdots + 2m + 2n + 2p + 1$.

This gives a value considerably above 600,000,000,000—a manifest absurdity. However, it is not necessary that all these cells should be produced, since the ratios would not be appreciably affected by some lines becoming crowded out. It is necessary, on the other hand, that all of the series shall be completed in every line which does live, since every female *Drosophila*,[2] which is of the proper constitution to be tested, shows linkage for every pair of genes tested.

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[2] The results discussed here deal only with the linkage in female flies.

Thus we are forced to assume an enormously complex series of cell divisions, many of them differential, proceeding with mathematical regularity and precision, but in a manner for which direct observation furnishes no basis. It seems to me that it is not desirable to assume such a complex series of events unless we have extremely strong reasons for doing so. I can see no sound reason for adopting the reduplication hypothesis. It apparently rests on two discredited hypotheses: somatic segregation, and the occurrence of members of the 3:1, 7:1, 15:1, etc., series of gametic ratios in more cases than would be expected from a chance distribution.

The chief advantage of the chromosome hypothesis of linkage which has been proposed by Morgan ('11), and which I have followed elsewhere, seems to me to be its simplicity. In addition it appeals to a known mechanism, and a mechanism toward which the experiments of Boveri, Herbst, Baltzer and others point as the correct one. It explains everything that any of the forms of the reduplication hypothesis does, and in addition offers a simple mechanical explanation of the fact that "secondary series" are always smaller than Trow's "special hypothesis" calls for them to be. On the reduplication hypothesis this fact must merely be accepted, for, I think, it can not be explained.

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